PATENT
Attorney Docket No. 4249.0002-05

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

John B. SULLIVAN et al.

Serial No. 08/405,454

Filed: March 15, 1995

For: ANTIVENOM COMPOSITION CONTAINING FAB FRAGMENTS (amended)

Group Art Unit: 1816

Examiner: Ron Schwadron, Ph.D.

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

FIRST DECLARATION OF FINDLAY E. RUSSELL, M.D., PH.D.
UNDER 37 C.F.R. § 1.132

I, Findlay E. Russell, M.D., Ph.D., do hereby declare and say as follows:

1. I am a citizen of the United States and am currently a resident of the United States.

2. I received a B.A. from Walla Walla College in 1941.

3. I received an M.D. from Loma Linda University in 1950.

4. I received a Ph.D. from the University of Santa Barbara in 1974.

5. I received an honorary L.L.D. from the University of Santa Barbara in 1978.

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6. I am currently Research Professor of Pharmacology and Toxicology at the University of Arizona in Tucson, Arizona.

7. I have held teaching and research positions in several universities and government agencies in the fields of physiology, neurology, pharmacology, toxicology, and toxinology. These positions are listed on my Curriculum Vitae, which is attached as Exhibit 1.

8. I currently hold positions in numerous societies in the fields of physiology, neurology, pharmacology, toxicology, toxinology, and herpetology. These positions are listed on my attached Curriculum Vitae and include the following:

Fellow, Royal Society of Medicine
Fellow, International Society of Toxicology (Pres. 1961-1966);
Fellow, Herpetology, Natural History Museum (London);
Member, American Academy of Clinical Toxicology
(Theines Award, 1965); and
Member, Western Pharmacology Society (Pres. 1972-1973).

9. I have received numerous honors and awards, which are listed on my attached Curriculum Vitae. Many of these honors and awards relate to my work with venoms, and they include the following:

Chairman, Ad Hoc Committee on Snakebite,
National Academy of Medicine, 1962;
Chairman, Ad Hoc Committee on Marine Fish Poisoning
World Health Organization, 1972, 1976;
Member, Ad Hoc Committee on Snake Antivenoms,
World Health Organization, 1969, 1979;
Co-Chairman, National Seminar on Protein Chemistry,
Snake Venom and Hormonal Protein, US-ROC,
National Science Foundation, 1978;
Editor, Toxicology Newsletter, 1955-1960;
Editor, Toxicon, 1962-1970; and
Corresponding member of Academy of Sciences of Yugoslavia, Slovenia.

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10. I have served as a consultant on venoms and venomous animals to the following organizations:

National Academy of Sciences;
American Medical Association;
American Association of Poison Control Centers;
U.S. Armed Forces;
International Red Cross;
National Science Foundation;
National Institutes of Health;
Office of Naval Research;
NASA;
FDA; and
the World Health Organization.

11. I am a coauthor of 370 papers, 26 textbook chapters, and 9 books in the fields of toxicology, toxicology, pharmacology, physiology, and medicine.

12. A substantial part of my 47-year professional career has been directed to research in the field of pharmacology and toxinology, particularly to research involving snake venoms, their *in vivo* effects in humans, and treatments for snake envenomation.

13. I am a co-inventor of U.S. Patent Application No. 08/405,454, filed March 15, 1995 ("the subject patent application").

14. I have read the subject patent application and the June 19, 1997, Office Action (Paper No. 29). I have been asked to provide the following comments regarding this patent application and Office Action.

SNAKE VENOMS

15. A venom is a toxic substance produced by a plant or animal in highly specialized cells or an organ and usually delivered through a biting or stinging act. Although venoms can be simple substances, as in some marine animals, in snakes

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they are often very complicated mixtures of individual toxins, including proteins of large and small molecular weights, phospholipases, hyaluronidase, collagenase, acidocologanase, l-amino acid oxidase, hydrolyses, nucleotideases, lipids, metalloproteins, free amino acids, steroids, aminopolysaccharides, amines, quinones, 5-hydroxytryptophan, and other substances. For example, snake venoms of the family Crotalidae comprise at least 20 different compounds. In some *Crotalus sp.* snake venoms, there may be 100 different protein fractions, 25 of which may be enzymes. Due to their complexity, the full composition of snake venoms is unknown.

16. Not only is the full composition of snake venoms unknown, but the pharmacological effects of some constituent toxins are unknown. Although the individual components of some snake venoms are known to have pharmacologic activities, including hematologic, cardiotoxic, neurotoxic, and other properties, each component may have more than one of these activities, and components may have different actions on different cell types. Furthermore, some of the more important reactions in humans to *Crotalus* envenomation are autopharmacologic or the result of synergisms between different venom components. As a result, of the at least 100 known components of *Crotalus* snake venoms, less than 20 compounds have known pharmacologic activities. Russell, F.E. (1980) *Snake Venom Poisoning* at p. 139 (attached as Exhibit 2).

17. Indeed, it would have been clear to a researcher in the field that we used the term "venom" in the subject patent application to mean a venom comprising several different toxins, not just a single toxin. Each venom discussed in the application

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contains several toxins. Furthermore, the application specifically discusses isolating specific venom proteins (toxins) from the snake venom. Specification at 6, last sentence. Accordingly, a researcher in the field would have understood from the subject patent application that we used the term "venom" in the subject patent application to mean a mixture of toxins, not a single toxin isolated from a venom.

18. The term "antivenin" was first used to identify the first antiserum for snake venom poisoning, and we specifically defined "antivenin" in the specification in this way:

> Antivenin is a suspension of venom-neutralizing antibodies prepared from the serum of animals (typically horses) hyperimmunized against a specific venom or venoms.

Specification at 4, lines 19-22. Although the terms "antivenin" and "antivenom" are often interchanged, researchers in the field now use the term "antivenom" because the World Health Organization ("WHO") has decided that "antivenom" is the preferred term. WHO/B5/80-1292 BLG/VEN/80.1 Rev. 1 (attached as Exhibit 3). Indeed, although I was one of the dissenters in the WHO vote and prefer the term "antivenin," I have previously indicated that the terms "antivenin" and "antivenom" are now interchangeable: "ANTIVENIN (ANTIVENENE, ANAVENIN, ANTIVENIMEUX, ANTIVENINIUM, ANTIVENOM) . . . ." Russell, F.E. (1988) Snake Venom Immunology: Historical and Practical Considerations. *J. Toxicol.-Toxin Rev.* 7(1), 1 (attached as Exhibit 4).

19. At the time of the application, the only commercially available antivenom for envenomation by North American snakes of the family Crotalidae was Antivenin (Crotalidae) Polyvalent (equine origin) (Wyeth Laboratories, Philadelphia, PA). Since

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this was the only commercially available antiserum for snakes in the United States, it was sometimes referred to as simply "antivenin." However, it would have been clear to a researcher in the field that our recitation of "antivenin" in the specification referred generically to all antivenins, not specifically to Wyeth's Antivenin (Crotalidae) Polyvalent (equine origin) because, among other reasons, we specifically referred to Wyeth's product as "ACP" in the application. E.g., specification at 2, line 11. Furthermore, we compared Wyeth's product to our claimed antivenom in the specification at page 23, lines 5-15.

Prior Treatment of Crotalidae Envenomation

20. Approximately 8,000 people are bitten by venomous snakes in the United States each year. Most of these people are bitten by *Crotalus*, a genus of the family Crotalidae. Before the advent of pharmacological methods of treating snake envenomation, it is estimated that envenomation by *Crotalus* resulted in approximately 7% mortality.

21. The most effective and most common treatment of Crotalidae envenomation is the administration of antivenom. The first reported use of a snake antivenom in humans occurred in the late 19th century. The only commercially available antivenom for North American Crotalidae is ACP, which first became available in 1947. Soon after the development of the first antivenoms, doctors recognized that they could elicit serum sickness, an allergic reaction to the antisera that was sometimes more deleterious than the venom. Over 75% of patients treated with ACP develop some manifestation of serum sickness. The problem of serum sickness can be so great

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that physicians may not administer antivenom for some cases of envenomation. Indeed, ACP can only be obtained in a kit that also contains test serum for possibly detecting serum sickness before administering the antivenom.

22. The serious deficit of serum sickness with antivenom has long contributed to extensive research on modifying existing antivenoms or developing new antisera. Since the serum sickness results from immune reactions of the patient to the immunoglobulin component of the antivenom, which actually binds to the venom toxins, much of this research focused on using fragments of immunoglobulin molecules that might not provoke a immune reaction.

23. As the figure attached as Exhibit 5 shows, a molecule of immunoglobulin comprises two heavy chains and two light chains with the heavy chains linked by two disulfide bonds at their hinge region. Each light chain forms an antigen binding site with the corresponding heavy chain at the end distant to the hinge region.

24. Cleavage of immunoglobulin with pepsin cleaves the IgG molecule below the disulfide bonds, resulting in a single Fc fragment and a single $F(ab)_2$ fragment (sometimes called an $F(ab)'_2$ fragment), which contains the two antigen binding sites. In contrast, cleavage of IgG with papain cleaves the immunoglobulin molecule above the disulfide bonds, resulting in a single, larger Fc molecule and two Fab fragments (sometimes called F(ab) fragments), each containing a single antigen binding site. Specification at 2, lines 25-43.

25. In the 1960s, researchers began experimenting with antivenoms comprising $F(ab)_2$ fragments. These became commercially available outside the U.S.

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in 1969. Although these $F(ab)_2$ antivenoms produced less serum sickness, as would be expected from their greater purity, such antivenoms appeared to some to be less effective than antivenoms comprising whole immunoglobulin. Consequently, Crotalidae antivenoms comprising $F(ab)_2$ fragments were not produced in the United States.

Antivenoms Comprising Fab Fragments Were Expected to Fail

26. As of 1984, no significant improvements in antivenoms had been made since some antivenoms comprising $F(ab)_2$ fragments became available in 1969. Significantly, although serum sickness had long been recognized as a major problem with antivenoms, and although smaller antibody fragments had long been known to be less immunogenic, no researcher developed an antivenom comprising the smaller Fab fragments. The development of antivenoms comprising antibody fragments stopped at the larger $F(ab)_2$ fragments because researchers in the field expected that Fab fragments would be less effective than $F(ab)_2$ fragments. Indeed, those researchers believed that Fab fragments might actually alter the toxicity of a Crotalidae venom.

27. Researchers in the field were concerned that antivenoms comprising Fab fragments would be less effective than antivenoms comprising $F(ab)_2$ fragments because: 1) the Fab fragments would not prevent the various venom toxins from binding to their site of action as well as the $F(ab)_2$ fragments; 2) the Fab fragments would not precipitate the various venom toxins; and 3) the Fab fragments would not neutralize sufficient venom toxin before being cleared because of their short half-life.

28. Immunoglobulins neutralize toxins in several ways. For example, they bind specifically to epitopes present on the toxins. In the case of a polyclonal

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antivenom, this may involve several epitopes present on more than one antigen. These antigen-antibody complexes are readily eliminated by the reticuloendothelial system, or by other mechanisms.

29. Since $F(ab)_2$ fragments contain two antigen binding sites, like whole immunoglobulin, it was suspected that they could more effectively bind to repeating antigenic determinants on large proteins than could Fab with only one binding site. Sell, S. (1987) *Basic Immunology: Immune Mechanisms in Health and Disease* at p. 89, Fig. 6-3 (attached as Exhibit 6). As a result, it was felt that while Fab fragments might bind to venom toxins, they would not be as effective as whole IgG or $F(ab)_2$ fragments.

30. Furthermore, researchers in the field expected that antivenoms comprising Fab fragments would not be as effective as antivenoms comprising $F(ab)_2$ fragments because Fab fragments have a shorter half life than $F(ab)_2$ fragments *in vivo*. Venom components are usually injected into subcutaneous tissues. Since many of the venom toxins are large, hydrophobic molecules, they are slowly released from these injection areas. This results in the "venom depot effect" where toxins are continuously released into the systemic circulation long after the initial bite.

31. The molecular weight of an Fab fragment is in the range of 45-55 ~~kd~~ kDa. As can be seen from Exhibit 5, the molecular weight of an $F(ab)_2$ fragment is over twice the molecular weight of an Fab fragment and approximately the same molecular weight as a whole IgG. As a result of these differences in molecular weights, Fab fragments are eliminated more quickly than $F(ab)_2$ fragments and whole IgG. Unbound Fab fragments

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are small enough to be removed by the renal system. Consequently they have a half-life of about 17 hours. Indeed, Fab fragments are completely eliminated in only 24 to 26 hours.

32. In contrast, $F(ab)_2$ fragments and whole IgG are too large to be eliminated by the renal system. Consequently they have a longer half-life, approximately 50 hours. The shorter half-life of Fab fragments compared to the half-life of venom, and compared to the half-life of $F(ab)_2$ fragments, led researchers in the field to expect that antivenins comprising Fab fragments would not be effective against Crotalidae envenomation.

33. Not only did researchers in toxinology and pharmacology believe that antivenoms comprising Fab fragments would be less effective than antivenoms comprising $F(ab)_2$ fragments, they suggested that antivenoms comprising Fab fragments might actually be harmful. They expected that the Fab fragments that did bind venom toxins during their short half-lives might not only fail to precipitate the venom toxins, but could actually redistribute the venom toxins to organs where the toxins might concentrate.

34. The binding of whole IgG, $F(ab)_2$ fragments, and Fab fragments to venom toxins is a dynamic process; even at a state of equilibrium, individual venom toxins are constantly being bound and released. The 45-55 ~~kd~~ kDa molecular weight of an Fab fragment is close to the upper filtration limit of the kidney. As stated, Fab can be cleared by the renal system, but the higher molecular weight $F(ab)_2$ fragments and

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whole IgG cannot. Whole IgG and $F(ab)_2$ fragments are instead cleared by the reticuloendothelial system and the liver, as are any unbound venom toxins.

35. In addition to allowing Fab fragments to be eliminated by the renal system, resulting in a shorter half-life, the small size of Fab fragments, as compared to $F(ab)_2$ fragments, also allows Fab fragments to be distributed to more parts of the body. Researchers in the field were concerned that this rapid clearance and larger volume of distribution of Fab fragments compared to $F(ab)_2$ fragments would result in a more systemic toxicity than a localized one.

36. Researchers in the field also speculated that the larger volume of distribution of the Fab fragments would allow Fab fragments to bind the venom toxins earlier than $F(ab)_2$ fragments. In addition, Fab fragments might bind venom toxins that $F(ab)_2$ fragments could not reach. As the bound Fab-toxin complex circulated throughout the body, however, Fab fragments could periodically release these toxins in their state of equilibrium. The unbound Fab fragments would be rapidly eliminated by the renal system, which could not eliminate the larger Fab-toxin complexes. Researchers, therefore, were concerned that such venom toxins would be redistributed to other areas of the body, perhaps concentrating in areas of high blood flow, especially the kidneys, heart, nervous system, and lungs. Thus, venom toxins that would have been released slowly from the bite site due to the venom depot effect would be redistributed to these areas of high blood flow. In other words, the Fab fragments would effectively serve as a vehicle, redistributing and concentrating these venom toxins from subcutaneous tissues, muscles and fat to the kidneys, heart, nervous system, and

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lungs, which would not have otherwise received a relatively high concentration of these toxins.

37. This concern was not merely a theoretical concern, as was later demonstrated by Faulstich *et al.* Faulstich *et al.* (1988) Strongly Enhanced Toxicity of the Mushroom Toxin ∝-Amanitin by an Amatoxin-Specific Fab or Monoclonal Antibody. *Toxicon* 26, 491(copy attached as Exhibit 7). Faulstich *et al.* conducted a series of studies attempting to treat ∝-amatoxin poisoning with Fab fragments. Alpha-amatoxin is a high molecular weight toxin that is similar to some snake venom toxins. As a high molecular weight toxin, ∝-amatoxin cannot be cleared by the renal system. Rather, like many snake toxins, it is cleared by the liver. Since ∝-amatoxin is concentrated in the liver after oral ingestion, it is primarily toxic to liver cells.

38. Faulstich *et al.* discovered that the Fab fragments did not decrease the toxicity of ∝-amatoxin in mice, but rather increased the toxicity of ∝-amatoxin by a factor of 50. Id. at 497. Furthermore, the Fab fragments resulted in ∝-amatoxin being specifically toxic to kidney cells rather than liver cells. This is exactly what one of ordinary skill in the art would have predicted. The Fab fragments bound the high molecular weight ∝-amatoxin, and then unbound it in their state of equilibrium at sites of high blood flow. This unbinding at sites of high blood flow, especially the kidneys, resulted in the ∝-amatoxin being concentrated in these tissues.

39. Similarly, Balthazar *et al.* conducted research on Fab fragments against digoxin. Balthazar *et al.* (1994) Utilization of Antidrug Antibody Fragments for the Optimization of Intraperitoneal Drug Therapy: Studies Using Digoxin as a Model Drug.

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J. Pharm. Exp. Ther. 268, 734 (attached as Exhibit 8). Digoxin is unlike most Crotalidae venom toxins; it is a very small molecule. Digoxin is small enough that the renal system can clear the Fab-digoxin complex. Since the renal system can filter the Fab-digoxin complex, the Fab did not redistribute and concentrate digoxin, as one of ordinary skill in the art would have predicted. Accordingly, Balthazar *et al.* found that F(ab) fragments effectively treated digoxin toxicity.

40. However, Balthazar *et al.* recognized the potential problems of Fab therapy for large toxins, like ∝-amatoxin and some Crotalidae venom toxins:

> First, the alteration of drug distribution which accompanies antibody drug complexation may result in a **potentiation of drug toxicities** or the development of **new drug toxicities in certain cases** . . . . The risk of **redistributing systemic toxicity**, rather than minimizing systemic toxicity, should be appreciated as a potential outcome of the proposed approach.

Id. at p. 738, paragraph bridging cols. 1 and 2 (emphasis added).

41. Accordingly, researchers in the field were concerned that treatment with an antivenom comprising Fab fragments would be a harmful treatment for high molecular weight toxins, not an advisable treatment, because the Fab fragments would redistribute high molecular weight toxins to areas of high blood flow, creating new toxicities and converting a localized toxicity into a systemic toxicity. Faulstich *et al.* confirmed this concern with a toxin that is of a similar molecular weight as many snake venom toxins.

42. Balthazar *et al.* reinforced this concern by showing that this effect did not occur with a low molecular weight toxin that the renal system could clear as part of an

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Fab-toxin complex. Indeed, despite the effectiveness of their treatment, Balthazar *et al.* specifically discussed their concern that Fab fragments might alter drug toxicities or redistribute systemic toxicities.

43. In sum, prior to our invention, researchers in the field did not have a reasonable expectation of success that an antivenom comprising Fab fragments to Crotalidae venom would be effective. Despite known problems with the only commercially available antisera for Crotalidae envenomation and much research since 1947, no researcher had developed an antivenom comprising Fab fragments. Furthermore, although $F(ab)_2$ fragments had been used in antivenoms since the late 1960s, those of ordinary skill in the art had not progressed beyond $F(ab)_2$ fragments to the smaller Fab fragments.

44. Even though Fab fragments were known to be highly effective in reducing the serum sickness, researchers in the field did not create a Crotalidae antiserum comprising Fab fragments because they were sure such a product would not work. Researchers in the field were concerned that such an antivenom would be ineffective because: 1) the Fab fragments could not stearically hinder the Crotalidae venom toxins from binding to their target; 2) the Fab fragments could not precipitate the venom toxins; and 3) the Fab fragments had too short a half-life *in vivo* to be able to bind some snake venom toxins. Furthermore, researchers in the field were concerned that such an antivenom might actually increase the toxicity of the venom by redistributing the more deleterious toxins.

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The Coulter *et al.* Reference

45. I understand that the Examiner has rejected the pending claims in Paper No. 29 over numerous references, including the Coulter *et al.* reference (Coulter *et al.* (1983) Simplified Preparation of Rabbit Fab Fragments. *J. Immun. Meth.* 59, 199 (attached as Exhibit 9)). For the above reasons, none of the references the Examiner has cited, alone or in combination, teach or suggest an antivenom comprising Fab fragments against a Crotalidae venom ~~with~~ would have a reasonable expectation of success.

46. However, the Coulter *et al.* reference merits individual mention in order to clarify the Examiner's understanding of it. Coulter *et al.* used textilotoxin, "a neurotoxin" and the primary toxin in the venom of the Australian brown snake (*Pseudonaja textilis*). Id. at 199, last sentence. The pending claims recite a snake of the genus *Crotalus*, a genus of the family Crotalidae. As can be seen from its name, the snake Coulter *et al.* used is not a member of the genus *Crotalus*, nor even of the family Crotalidae. Rather, it is a member of the genus *Pseudonaja*. Indeed, Cassarett and O'Doul's Toxicology teaches that Coulter *et al.*'s snake is an elapid, Russell (1996) Toxic Effects of Animal Toxins. In *Casarett and Doull's Toxicology: The Basic Science of Poisons*, (5th Ed.) at p. 802 (attached as Exhibit 10), and the elapids are of the family Elapidae, not Crotalidae. *Snake Venom Poisoning* at p. 5.

47. Furthermore, textilotoxin is simply **a single toxin** from Australian brown snake venom. As I discussed above, the terms "antivenom" and "antivenin" mean an immunotherapy mixture against a snake **venom**, not simply a single snake toxin. As I have also noted, snake venoms are complex mixtures of many substances, including

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many different toxins. Snake venoms, particularly those of snakes of the family Crotalidae, are composed of many different toxins. Each of the individual toxins can act synergistically *in vivo* and may also induce autopharmacologic reactions. Indeed, basic toxicology texts caution against extrapolating results from individual venom toxins to whole venoms. Toxic Effects of Animal Toxins at p. 802; *Snake Venom Poisoning* at p. 168. Accordingly, one would not have expected Coulter *et al.*'s results with Fab to a single **toxin** to predict similar results with Fab to a Crotalidae snake **venom**, including a *Crotalus* snake **venom**.

48. Most importantly, Coulter *et al.* did not treat envenomation with their Fab fragments. Rather, Coulter *et al.* first mixed textilotoxin with their Fab fragments *in vitro*. Coulter *et al.* at p. 901, 3rd full paragraph. Coulter *et al.* then injected the already bound Fab-textilotoxin complex intravenously. This treatment with Fab fragments resulted in neutralization that was essentially equivalent to the treatment with the IgG fragments, just as one would have expected. Since the Fab-textilotoxin mixture was injected intravenously, the Fab did not have the opportunity to redistribute and concentrate the textilotoxin in high blood flow parts. Accordingly, the Coulter *et al.* reference would not have provided a reasonable expectation of success for an antivenom comprising Fab fragments to any venom toxins.

49. Similarly the observation of Coulter *et al.* that enzyme-linked immunoabsorbent assays with higher sensitivity had been claimed when Fab is used instead of whole IgG would not have suggested combining any of the cited references with a reasonable expectation of success. As in the case of Coulter *et al.*'s actual

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results, *in vitro* observation would have been irrelevant to the lack of expectation of success *in vivo* since the reasons one would not have had a reasonable expectation of success were due to the expected *in vivo* action of the Fab fragments.

50. Indeed, Sorkine *et al.* conducted a similar experiment in 1983 by mixing Fab fragments with a venom of a non-Crotalidae snake prior to injection into a mouse, and they obtained similar results. Sorkine *et al.* (1995) Comparison of $F(ab')_2$ and Fab Efficiency on Plasma Extravasation Induced *Viper aspis* Venom. *Toxicon* 33, 257 (attached as Exhibit 11). This treatment resulted in a considerable reduction in capillary permeability. However, the Fab fragments were much less effective when they were administered *in vivo* separately from the venom. As Sorkine *et al.* state "these data showed firstly that the *in vitro* neutralization of the venom by immunoglobulin fragments does not reflect their *in vivo* efficiency." Id. Thus, the Sorkine *et al.* reference shows that one would not have expected Coulter *et al.*'s *in vitro* neutralization results to predict the effectiveness of ~~antivenins~~ antivenoms comprising Fab fragments *in vivo*.

51. In 1984, no clinician or researcher expected that a Crotalidae snake antivenom comprising Fab fragments would be effective in treating Crotalidae snake envenomation. Thirty-seven years of research primarily aimed at reducing the serum sickness produced by ACP and fifteen years of research since the first, disappointing $F(ab)_2$ antivenom had convinced those of ordinary skill in the art that a Crotalidae antivenom comprising Fab fragments would be less effective than the known antivenoms. Furthermore, those of ordinary skill in the art actually expected a Crotalidae antivenom comprising Fab fragments to increase the lethality of the snake

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venom. Accordingly, there was no expectation of success in using any Crotalidae antivenom comprising Fab fragments to treat Crotalidae envenomation, let alone an expectation of success in using a *Crotalus* antivenom comprising Fab fragments to treat *Crotalus* envenomation.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and, further, that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine, imprisonment, or fine and imprisonment under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of this application or any patent issuing therefrom.

Date: April 30, 1998

By: Findlay E. Russell M.D. Ph.D.
Findlay E. Russell, M.D., Ph.D.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Serial No. 08/405,454

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For: ANTIVENOM COMPOSITION CONTAINING FAB FRAGMENTS (amended)

Group Art Unit: 1816

Examiner: Ron Schwadron, Ph.D.

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

SECOND DECLARATION OF FINDLAY E. RUSSELL, M.D., PH.D. UNDER 37 C.F.R. § 1.132

I, Findlay E. Russell, M.D., Ph.D., do hereby declare and say as follows:

1. I am one of the joint inventors of the subject matter disclosed in U.S. patent application Serial No. 08/405,454.

2. Attached hereto as Exhibit 1 are claims 40-49.

3. On information and belief, claims 40-49 of Exhibit 1 are pending in U.S. patent application Serial No. 08/405,454.

4. I have examined claims 40-49 of Exhibit 1, and I believe that I am a joint inventor of the subject matter of these claims.

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5. I am a coauthor of an article identified as Sullivan, Russell *et al.* (1984) Protection Against Crotalus Venom Lethality by Monovalent, Polyclonal F(ab) Fragments: In Search of a Better Snake Trap. *Veterinary and Human Toxicology* 26, 400 ("the Sullivan, Russell *et al.* article").

6. I am a joint inventor of the subject matter disclosed in the Sullivan, Russell *et al.* article.

7. I understand that the Examiner cited the Sullivan, Russell *et al.* article against claims 40-49 of U.S. patent application Serial No. 08/405,454 because Ned Egan and Michael Owens are named as coauthors of the Sullivan, Russell *et al.* article, but they are not named as coinventors of U.S. patent application Serial No. 08/405,454. I also understand that the Examiner asserted that the subject matter claimed in claims 40-49 was not invented by the inventors named in the application.

8. The experimental work described in the Sullivan, Russell *et al.* article was either conducted by John B. Sullivan or myself, or it was performed under our direction or supervision.

9. Ned Egan and Michael Owens performed the isoelectric focusing and antibody separation required to obtain the F(ab) fragments John B. Sullivan and I used in the work reported in the Sullivan, Russell *et al.* article. Dr. Egan performed experimental work under my direction or supervision. Dr. Owens performed experimental work under John B. Sullivan's direction or supervision.

10. Ned Egan and Michael Owens did not make an inventive contribution to the experimental work described in the Sullivan, Russell *et al.* article, nor did they make an

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inventive contribution to the subject matter disclosed or claimed in U.S. patent application Serial No. 08/405,454. They are not joint inventors of this subject matter.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and, further, that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine, imprisonment, or fine and imprisonment under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of this application or any patent issuing therefrom.

Date: April 30, 1998

By: Findlay E. Russell M.D., Ph.D.
Findlay E. Russell, M.D., Ph.D.

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Pending Claims of Serial No. 08/405,454

40. An antivenom composition comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier, wherein said venom comprises more than one toxin.

41. The antivenin composition of claim 40, wherein an antibody source for said Fab fragments is IgG(T).

42. The antivenin composition of claim 40, wherein an antibody source for said Fab fragments is polyvalent IgG(T).

43. The antivenin composition of claim 40, wherein said Fab fragments are derived from IgG(T).

44. The antivenin composition of claim 40, wherein said Fab fragments are derived from polyvalent IgG(T).

45. Fab fragments which bind specifically to a venom of a snake of the Crotalus genus, and which are essentially free from contaminating Fc as determined by

immunoelectrophoresis using an anti-Fc antibody, wherein said venom comprises more than one toxin.

46. The Fab fragments of claim 45, wherein an antibody source for said Fab fragments is IgG(T).

47. The Fab fragments of claim 45, wherein an antibody source for said Fab fragments is polyvalent IgG(T).

48. The Fab fragments of claim 45, wherein said Fab fragments are derived from IgG(T).

49. The Fab fragments of claim 45, wherein said Fab fragments are derived from polyvalent IgG(T).